Translation

PCT/FR2003/002667

PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|---|---|
| Applicant's or agent's file reference CP/60.769PCT | FOR FURTHER ACTION | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) |
| International application No. PCT/FR2003/002667 | International filing date (*day/month/year*) 08 septembre 2003 (08.09.2003) | Priority date (*day/month/year*) 06 septembre 2002 (06.09.2002) |
| International Patent Classification (IPC) or national classification and IPC C12Q 1/34, G01N 33/68, C07K 16/40 | | |
| Applicant INSTITUT NATIONAL DE LA SANTE ET DE LA RECHERCHE MEDICALE (I.N.S.E.R.M.) | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

| | |
|---|---|
| Date of submission of the demand 06 avril 2004 (06.04.2004) | Date of completion of this report 25 November 2004 (25.11.2004) |
| Name and mailing address of the IPEA/EP<br><br>Facsimile No. | Authorized officer<br><br>Telephone No. |

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002667

## I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:
pages 1-30, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:
pages 1-22, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the drawings:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:
pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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International application No.
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**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-7, 9

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 1-7 are so unclear that no meaningful opinion could be formed *(specify)*:

See supplemental sheet

☒ the claims, or said claims Nos. 9 are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for said claims Nos. _____.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**Supplemental Box**
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III

1. Since the subject matter of claims 1 to 7 is so unclear (PCT Article 6) and the subject matter of claim 7 is not sufficiently supported by the description for the invention to be implemented (PCT Articles 5 and 6), no opinion can be given in the present international preliminary examination report with regard to novelty, inventive step and industrial applicability (see points 2 to 4 in Box V).

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

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PCT/FR 03/02667

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|---|---|---|---|
| Novelty (N) | Claims | 8, 10-19 | YES |
| | Claims | 20-22 | NO |
| Inventive step (IS) | Claims | 8, 10-19 | YES |
| | Claims | 20-22 | NO |
| Industrial applicability (IA) | Claims | 8, 10-19 | YES |
| | Claims | | NO |

2. Citations and explanations

Reference is made to the following documents:

Schagger D1: European Journal of Biochemistry / Febs. Germany 1 Feb 1995 (01-02-1995), 227(3), 916-921

Kim D2: CMLS Cellular and Molecular Life Sciences (11-2000), 57(12), 1810-1816

LeFebvre D3: Journal of Biological Chemistry (02-03-2001), 276(9), 6789-6796

Chang D4: Journal of Biological Chemistry (08-03-2002), 277(10), 8388-8394

MOSER D5: Proceedings of the National Academy of Sciences of USA, National Academy of Science. Washington, USA (16-03-1999), 96(6), 2811-2816

MOSER D6: US-B1-6444431

2. The subject matter of claim 1 is not clear (PCT Article 6) for the following reasons:

2.1 The wording of claim 1 does not clearly define the subject matter for which protection is sought. Indeed, it is not clear whether the subject matter of claim 1 relates to the use of the ATP synthase α chain as markers for the neurodegenerative process (see also the objection raised in point 3) or to the

modified ATP synthase α chain as such.

2.2 Furthermore, said claim fails to comply with the requirements of PCT Article 6, since the subject matter of the claim is defined in terms of the result to be achieved, i.e. an ATP synthase α chain that has been pathologically modified as a result of the neurodegenerative process. Such wording is only permitted in exceptional cases, as defined in the PCT Examination Guidelines, paragraph III-4.7. In the present case such wording is not permitted, since the ATP synthase α chain can be defined in concrete terms, by clearly defining the modifications concerned (see, however, point 4). Since the scope of the claim must be as precise as possible (PCT Examination Guidelines, paragraph III-4.7), said claim must contain the modifications identified by the applicant, which therefore constitute an essential feature of the invention that is not obvious to a person skilled in the art.

3. The subject matter of claim 1 also fails to meet the requirements of PCT Articles 5 and 6 for the following reasons:
the subject matter of claim 1 relates to neurodegenerative process markers consisting of the ATP synthase α chain modified by said process. However, serious doubts exist as to whether the subject matter of claim 1 applies to the full scope of said claim.
The description only demonstrates the involvement of the modified ATP synthase α chain in Alzheimer's disease. Said description does not demonstrate its involvement in all known neurodegenerative

processes, such as Parkinson's disease, for example. Hence, in the absence of technical details and/or examples demonstrating the involvement of the modified ATP synthase α chain in all known neurodegenerative processes, serious doubts exist as to whether the subject matter of claim 1 is applicable to the full scope of said claim. Merely stating that said modified ATP synthase α chain is involved in all neurodegenerative processes is not sufficient.

Said claim 1 is not sufficiently supported by the description (PCT Article 6) to allow a person skilled in the art to carry out the invention over the full scope of said claim (PCT Article 5).

In the light of PCT Articles 5 and 6, this objection also applies to claims 3, 8, 10, 15, 17, 18 and 19.

4. Claims 2, 4 and 6 are also unclear (PCT Article 6). Said claims relate to the modifications of the ATP synthase α chain. However, said modifications (functional or structural) are not defined. Insolubility or aggregation are the result of said modifications. In the absence of said features, it is impossible to differentiate the claimed ATP synthase α chain from the ATP synthase α chain, which is well known from the prior art. Similarly, the location of the ATP synthase α chain in the cytoplasm does not constitute a characterising feature of said protein that enables it to be differentiated from the ATP synthase α chain known from the prior art.

5. Setting aside the objection raised above (see point 3), since the particular combination of features of claim 8 is not disclosed in the prior art, the subject matter of said claim is considered novel within the meaning of PCT Article 33(2).

Furthermore, the subject matter of claim 8 involves an inventive step within the meaning of PCT Article 33(3) for the following reason:
D1 and D2 are considered to be the closest prior art. Said documents disclose the involvement of the ATP synthase α chain in Alzheimer's disease (abstract).
The subject matter of claim 8 differs from D1 and D2 in that the presence of the ATP synthase α chain is detected in insoluble form, in aggregate form or in the cytoplasm.
The technical effect of this difference is that a novel method is offered for detecting and/or diagnosing Alzheimer's disease.
It appears that the applicant is the first to have identified the various forms of the ATP synthase α chain involved in Alzheimer's disease. The applicant has demonstrated that the ATP synthase α chain is found in insoluble form, in the form of aggregates or in the cytoplasm in patients suffering from Alzheimer's disease. Having made this observation, the applicant developed a novel method for detecting and/or diagnosing said disease.

The subject matter of claim 8 therefore meets the requirements of PCT Article 33(3).

For the same reasons, the subject matter of claims

15, 16 and 19 also involves an inventive step (see, however, points 7 to 9 below).

6. The subject matter of claim 9 fails to meet the requirements of PCT Articles 5 and 6. Said claim relates to the use of antibodies directed against modifications to the ATP synthase α chain. However, the description describes no antibody that specifically recognises a modified ATP synthase α chain. Furthermore, since said modifications are not described in the description (the effects of said modifications are described, namely the insolubility or the aggregation of said protein), a person skilled in the art would not be able to produce antibodies against said modifications, as claimed in claim 9.
Said claim 9 is therefore not sufficiently supported by the description (PCT Article 6) to allow a person skilled in the art to carry out the invention over the full scope of said claim (PCT Article 5).

7. The subject matter of claim 15 is not clear (PCT Article 6). The application of a method corresponds to the method *per se*. The subject matter of claim 15 is an alternative to the subject matter of claim 8 and should therefore be dependent on said claim 8.

8. The subject matter of claim 16 fails to meet the requirements of PCT Articles 5 and 6. Said claim relates to a maturation signal fault and/or a post-translational modification anomaly, without stating what said fault or anomaly is. Said faults or anomalies may be so numerous and so vast that a person skilled in the art would not know which to

choose. Furthermore, none of these modifications would lead to a protein that is insoluble, aggregated or located in the cytoplasm.
Said claim 16 is not sufficiently supported by the description (PCT Article 6) to enable a person skilled in the art to implement the invention over the full scope thereof (PCT Article 5).

8.1 Since the term "animal" encompasses a human being, most national or regional jurisdictions consider such an animal model to be contrary to morality.

9. The subject matter of claim 19 is not clear (PCT Article 6). Since the diagnostic kit is not defined by technical features characterising said kit, the subject matter and the extent of said claim are not clearly defined.
A lack of clarity (PCT Article 6) also arises from the fact that it is the detection of the modified ATP synthase α chain that enables Alzheimer's disease to be diagnosed and not detection of the ATP synthase α chain.

10. The subject matter of claim 20 is not novel (PCT Article 33(2)). Since the antigen determinants of the protein are not defined, the possibility of the antibodies described in the prior art binding to the same antigens of the ATP synthase α chain cannot be ruled out (D3, page 6790; D4, page 8390; D5, page 2812).

11. For the same reasons as mentioned above, the subject matter of claims 21 and 22 is also not novel (PCT Article 33(2)), since D6 already describes a kit

including antibodies directed against the ATP synthase α chain and the subunits thereof (column 9, lines 22 to 32).

12. The subject matter of claim 22 is not clear (PCT Article 6) in that the reagents contained in the kit are not defined by technical terms. Consequently, neither the subject matter nor the extent of the protection sought can be clearly characterised.